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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,844	09/30/2003	Marvin P. Loeb	TDYNE-295-Con.	6900

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,844	LOEB, MARVIN P.	
	Examin r	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21 and 23-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21 and 23-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response and the change of address dated 10-14-04 are acknowledged.

Claims included in the prosecution are 1-19, 21 and 23-40.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-19, 21 and 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 461 662 or Kanno (5,374,715) or MacDonald (4,532,089) or WO 95/09610 individually or in combination, further in view of Li (5,641,508.

EP discloses giant liposomes of diameter of about 10 microns containing inorganic compounds, enzymes and other pharmaceuticals. According to EP, the liposomes can be formed from phospholipids such as phosphatidylcholine and phosphatidylethanolamine. EP further teaches the inclusion of cholesterol (note the abstract, page 4, lines 34-54 and Examples). Although EP teaches generic phosphatidylcholine and phosphatidylethanolamine, it does not specify the fatty acids present in these phospholipids such as those claimed (oleic acid in dioleoyl PE and palmitic acid in dipalmitoyl PC). EP is also silent with respect to the ratios.

Kanno similarly discloses giant proteoliposomes having instant sizes. The liposomes contain proteins, enzymes and receptor proteins. According to Kanno, the liposomes can be formed from phospholipids such as phosphatidylcholine and phosphatidylethanolamine. Kanno further teaches the inclusion of cholesterol (note the abstract, col. 5, line 19 through col. 6, line 17; col. 18, lines 49-62 and examples). Although Kanno teaches generic phosphatidylcholine and phosphatidylethanolamine, it does not specify the fatty acids present in these phospholipids such as those claimed (oleic acid in dioleoyl PE and palmitic acid in dipalmitoyl PC). Kanno is also silent with respect to the ratios.

MacDonald discloses liposomes having 10-50 micron diameters for the delivery of drugs and proteins such as enzymes. The liposomes are made from bilayer forming phospholipids (note the abstract, col. 1, line 53 through col.4, line 58 and Examples). What are lacking in MacDonald are the teachings of instant specific phospholipids, cholesterol and the ratios.

WO discloses giant liposomes having sizes up to 50 microns and containing a variety of active agents, which include plant and animal cells and microorganisms, cytokines, enzymes, antigens and antibodies. The liposomes are formed using phospholipids such as phosphatidylcholines (note the abstract, pages 9, 11-12, Examples and claims). WO does not teach instant phospholipids and is also silent with respect to the ratios.

Li while disclosing liposomal compositions teaches that liposomes can be formed using phospholipids containing specific fatty acid moieties. The specific phospholipids

taught by Li are dioleoyl PE and dipalmitoyl PC. Li further teaches that the amounts of the individual phospholipids can be varied and mixtures of phospholipids having preselected amounts of individual phospholipids results in liposome compositions having advantageous activity and stability of activity. The molar ratios of DPPC to DOPE taught by Li are 2:5 to 5:2 and the composition further contains cholesterol (abstract, col. 11, line 15 through col. 12, line 12, Examples and claims 6 and 7).

The use of phospholipids with specific fatty acids moieties in them, such as DPPC and DOPE in the giant liposomes of EP, Kanno or MacDonald would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success since Li teaches that these also form liposomes. Varying the ratios of these lipids would have been obvious to one of ordinary skill in the art since Li teaches that one can vary the ratios. Although the references are silent with respect to the residence time in a body fluid, the burden is upon applicant that it is different for the prior art liposomes since one would expect similar time profiles since they are made from phospholipids.

EP, MacDonald, Kanno and WO do not teach the method of administration of the liposomes. However, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to choose a specific mode of administration to obtain the best possible results. The references do not teach all of the claimed active agents such as growth factors and bone marrow cells. However, in view of the generic teachings and the guidance provided in the preparation of liposomes by the prior art, it is deemed obvious to one of ordinary skill in the art to encapsulate any active material

including cells and growth factors and cells with the expectation of obtaining similar encapsulation.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the primary references do not teach or suggest the claimed liposome constituents and the claimed ratios and collectively none of the references in the rejection could have suggested instant invention. Applicant further argues that the secondary reference of Li does not cure the shortcomings of the primary references. In particular, applicant argues that the preferred ratios taught by Li on col. 12, line 12 are 5:2:3 which is far removed from instant 7:3:5. These arguments are not persuasive. First of all, the primary references teach the formation of giant liposomes from bilayer forming phospholipids such as phosphatidylcholine and phosphatidylethanolamine and the examiner agrees that these references do not teach the claimed ratios. However, as pointed out in the previous action, one of ordinary skill in the art would be motivated to change the amounts of the phospholipids based on Li's teachings that the amounts of the individual phospholipids can be varied and mixtures of phospholipids having preselected amounts of individual phospholipids results in liposome compositions having advantageous activity and stability of activity. The examiner disagrees with applicant with regard to the argument that the ratios taught by Li are far removed from instant 7:3:5. First of all, Li teaches the ratio ranges of 2: 5 to 5:2 with respect to the phospholipids. Secondly, the preferred ratios 5:2:3 of Li when converted by the multiplication with a factor of 1.4 (7 divided by 5) are 7:2.8:4.2 which

are closer to instant ratios. Applicant has not shown any unexpected results obtained by varying the basic teachings of prior art.

3. Claims 1-19, 21 and 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 461 662 or Kanno (5,374,715) or MacDonald (4,532,089) or WO 95/09610 individually or in combination, in view of Li (5,641,508) as set forth above, further in combination with Ostro (American Journal of Hospital Pharmacy).

The teachings of EP, Kanno, MacDonald, WO and Li have been discussed above. As pointed out above, the references are silent with respect to the residence time in a body fluid.

Ostro teaches that half-life of smaller liposomes is in hours and that of large liposomes (MLVs) is in minutes (note page 1581, col. 1). One skilled in the art would be using the liposomes of instant sizes if the desired goal is to release the components rapidly since Ostro teaches that half life of large liposomes is in minutes.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments with regard to the primary references. The only argument regarding Ostro is that a mere teaching that the half-life or relatively larger liposomes is in minutes would not have suggested to one of ordinary skill in the art the specific limitations of the present claims. This argument is not found to be persuasive since the primary references are suggestive of the variations in the ratios of the phospholipids in forming the liposomes and one of ordinary skill in

the art would be motivated to prepare giant liposomes if the desired goal is to have a liposome populations whose half-life is in minutes based on the teachings of Ostro.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK